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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/523,886	03/13/2000	David J. Grdina	P-01904US1	6435

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	18

DATE MAILED: 02/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/523,886	Grdina et al.
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Feb 7, 2003* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see NOTE below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____

3. ☐ Applicant's reply has overcome the following rejection(s):

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
Applicants argue that Milas teaches the use of WR-2721 to reduce enhanced metastasis associated with radio- and chemotherapy but does not teach any effects on metastasis in the absence of radio or chemotherapy (amendment,

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____

Claim(s) objected to: _____

Claim(s) rejected: *1, 3-7, 9-13, and 23-33*

Claim(s) withdrawn from consideration: _____

8. ☐ The proposed drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ .

10. ☐ Other:

DETAILED ACTION

Continued from Advisory Action:

pages 6-7). This is not found persuasive because of the reasons set forth in the preceding Official actions mailed 5-1-02 (Paper No. 13) and 12-10-02 (Paper No. 16) and that the claims encompass reducing the number of metastases in an animal having a primary tumor whether the metastases is caused by the primary tumor or induced by radio- or chemotherapy. The metastases is the metastases **in an animal** exhibiting a primary tumor. The claims do not specify the metastases has to be caused by said primary tumor. The metastases can be the spontaneous metastases induced by cyclophosphamide (CY) and whole body irradiation (WBI) in mice with fibrosarcoma, which is a primary tumor. Further, the dose of 10mg/kg to 150mg/kg is in the range of subcytoprotective dose and the specification states the term "subcytoprotective dose" refers to an amount that is **too low to** prevent cell killing and/or loss of function in normal tissues exposed to **radiation and chemotherapy**" (see specification, page 6). Thus, the doses specified in the claims is associated with radiation and chemotherapy and the teaching of Milas is relevant to the claimed invention. In addition, whether the metastases is caused by the primary tumor or by radio- or chemotherapy, the teachings of Milas and Kanclerz indicates that it was unpredictable at the time of the invention whether various aminoalkylphosphorothioates, such as WR-2721, or active metabolite thereof would be able to reduce the number of metastases in an animal having various types of primary tumors or to reduce the number of metastases caused by

various types of tumors *in vivo*. Milas reports that the degree of tumor radioprotection afforded by WR-2721 varies with the type of tumor and assay endpoint. Kanclerz teaches when the radioprotector WR-2721 was given in fractioned schedules in three different doses (0.05g/kg, 0.1g/kg and 0.2g/kg for 10 consecutive days) a slight enhancement of **lung metastases** and suppression of **extrapulmonary metastases** was observed. Kanclerz measures **incidence of metastases** in the lungs and in other organs and shows WR-2721 **decreases incidence of metastases in adrenals** at highest dosage and WR-2721 at 0.4g/kg **inhibits lymph node metastases**. Thus, it would require one skilled in the art at the time of the invention to practice over the full scope of the invention claimed.

Applicants argue that the specification teaches examples f various tumors including sarcoma SA-NH, and the adenocarcinoma Mca-K and Oca-1 (amendment, p. 7). This is not found persuasive because of the reasons set forth in the preceding Official actions mailed 5-1-02 (Paper No. 13) and 12-10-02 (Paper No. 16) and the reasons set forth above. Further, sarcoma and adenocarcinoma are only two types of tumors, there are numerous other types of tumors, such as leukemia, melanoma, retinoblastoma, glioma and neuroblastoma etc.

Applicants argue that the Action relies on the mere statement that the specification fails to provide adequate guidance and evidence for use of the claimed invention *in vivo* but fails to provide reasoning and evidence for non-enablement (amendment, p. 8). This is not found persuasive because of the reasons set forth in the preceding Official actions mailed 5-1-02 (Paper No. 13) and 12-10-02 (Paper No. 16) and the reasons set forth above. The Action does provide

reasoning and evidence that it was unpredictable at the time of the invention whether various aminoalkylphosphorothioates, such as WR-2721, or active metabolite thereof would be able to reduce the number of metastases in an animal having various types of primary tumors or to reduce the number of metastases caused by various types of tumors *in vivo*, and the specification fails to provide sufficient enabling disclosure for the full scope of the claimed invention.

Applicants argue that the effectiveness of the current invention against various tumors has been established (amendment, p. 8). This is not found persuasive because of the reasons set forth in the preceding Official actions mailed 5-1-02 (Paper No. 13) and 12-10-02 (Paper No. 16) and the reasons set forth above.

Applicants argue that claim 1 does not recite or require induction or enhancement of metastases as taught by Milas and does not recite or require treating established metastases taught by Kanclerz. Applicants argue that treatment of induced metastases by radio- or chemotherapy is different from treatment to inhibit metastases or reduce the number of metastases (amendment, p. 11, 12). This is not found persuasive because of the reasons set forth in the preceding Official actions mailed 5-1-02 (Paper No. 13) and 12-10-02 (Paper No. 16). As discussed above, the claims encompass reducing the number of metastases in an animal having a primary tumor whether the metastases is caused by the primary tumor or induced by radio- or chemotherapy. The metastases is the metastases **in an animal** exhibiting a primary tumor. The claims do not specify the metastases has to be caused by said primary tumor. The metastases can be the spontaneous metastases induced by cyclophosphamide (CY) and whole body irradiation (WBI) in

mice with fibrosarcoma, which is a primary tumor. Milas does teach that WR-2721 greatly reduces the spontaneous metastases induced by cyclophosphamide (CY) and whole body irradiation (WBI) in mice with fibrosarcoma injected i.v. into said mice.

Applicants argue that Milas teaches the use of WR-2721 as a radioprotector used in combination with radiotherapy or chemotherapy and Kanclerz teaches growth inhibitory effects of WR-2721 and the results of Kanclez are ambiguous in the dosage range 0.05g/kg, 0.1g/kg and 0.2g/kg and teach away from the invention (amendment, p 12). This is not found persuasive because of the reasons set forth in the preceding Official actions mailed 5-1-02 (Paper No. 13) and 12-10-02 (Paper No. 16) and the reasons set forth above. Milas does teach that WR-2721 greatly reduces the spontaneous metastases induced by cyclophosphamide (CY) and whole body irradiation (WBI) in mice with fibrosarcoma. Kanclerz teaches when WR-2721 was given in fractioned schedules in three different doses (0.05g/kg, 0.1g/kg and 0.2g/kg for 10 consecutive days) suppression of **extrapulmonary metastases** was observed. Kanclerz measures **incidence of metastases** in the lungs and in other organs and shows WR-2721 **decreases incidence of metastases in adrenals** at highest dosage and WR-2721 at 0.4g/kg **inhibits lymph node metastases**. Figure 4 of Kanclerz does not teach away from the claimed invention. The effectiveness of WR-2721 on metastases depends on where the metastases is measured. Metastases in sacral and paraaortic nodes is greatly inhibited only at 0.2g/kg of WR-2721, however, metastases in adrenals is greatly inhibited at all WR-2721 concentrations used, i.e. 0.05g/kg, 0.1g/kg and 0.2g/kg. The concentrations of WR-2721 at 0.05g/kg and 0.1g/kg are

within the range of 10mg/kg to 150mg/kg recited in the claims. Thus, Kanclerz does not teach away from the claimed invention.

Applicants argue that there is no motivation or suggestion to combine Kanclerz and Milas references and even if they are combined neither reference describe methods of inhibiting metastases or reducing the number of metastases (amendment, p. 13). This is not found persuasive because of the reasons set forth in the preceding Official actions mailed 5-1-02 (Paper No. 13) and 12-10-02 (Paper No. 16) and the reasons set forth above. Milas teach that WR-2721 at 400mg/kg greatly reduces the spontaneous metastases induced by cyclophosphamide (CY) and whole body irradiation (WBI) in mice with fibrosarcoma. Kanclerz teaches that metastases in adrenals is greatly inhibited at all WR-2721 concentrations used, i.e. 0.05g/kg, 0.1g/kg and 0.2g/kg. The concentrations of WR-2721 at 0.05g/kg and 0.1g/kg are within the range of 10mg/kg to 150mg/kg recited in the claims. Thus, one ordinary skill in the art would be motivated to use WR-2721 at 0.05g/kg and 0.1g/kg to reduce the number of metastases or to inhibit metastases in an animal having a primary tumor with reasonable expectation of success.

Applicants argue that one ordinary skill in the art would not know how to use the claimed dose of aminoalkylphosphorothioates or active metabolites thereof to inhibit or reduce metastases and have no reasonable expectation of success (amendment, p. 13). This is not found persuasive because of the reasons set forth in the preceding Official actions mailed 5-1-02 (Paper No. 13) and 12-10-02 (Paper No. 16) and the reasons set forth above.

Applicants cite page 310 left column of Kanclerz reference and argue that "The statement that "suppression of extrapulmonary metastases was observed," in no way provides evidence of inhibition of metastases due to the fact that metastases has occurred prior treatment. One can not inhibit something that has already occurred". Applicants further argue that the extrapulmonary tissue was weighed after treatment and no counting of metastases was performed (amendment, p. 14, 15). This is not found persuasive because of the reasons set forth in the preceding Official actions mailed 5-1-02 (Paper No. 13) and 12-10-02 (Paper No. 16) and the reasons set forth above. In Kanclerz reference, metastases was induced by the established primary tumors in the tail of mice and the effect of WR-2721 on metastases from the primary tumor, which was removed before treatment of WR-2721, was observed. The effect of WR-2721 on metastases of tumor cells from the primary tumor to distant site of the mice can be measured only when the metastases does occur. If the metastases does not occur, it is unclear how one can test whether WR-2721 can inhibit metastases or not. Testing of WR-2721 **before** the occurrence of metastases in an animal is to test whether WR-2721 can **prevent** metastases, which is different from inhibiting metastases or reducing number of metastases. Weighing the extrapulmonary tissues is a way to measure whether WR-2721 can inhibit or reduce the number of metastases because when tumor cells from primary tumor in the tail metastasize to distant site of mice the tumor cells can proliferate to form tumors that would increase the weight of the tissue at that site. Thus, weighing the extrapulmonary tissue does show whether the treatment of WR-2721 causes inhibition of metastases or reduction in the number of metastases. Further, Kanclerz measures

incidence of metastases in the lungs and in other organs and shows WR-2721 **decreases incidence of metastases in adrenals** at highest dosage and WR-2721 at 0.4g/kg **inhibits lymph node metastases**.

Applicants argue that WR-2721 has been shown to be cytotoxic *in vivo* and WR-2721 is a general cell growth inhibitor. Applicants further argue that Kanclerz reference does not show whether the number of metastases is reduced or metastases is inhibited, and Figure 4 of Kanclerz reference shows that "the dose of 0.05g/kg is not significantly different from the untreated control organ weights. In two out of the four organ endpoints used, only the 2g/kg dose, which is beyond the 150mg/kg recited in the claims, is significantly different from the control values" (amendment, p. 15, 16). This is not found persuasive because of the reasons set forth in the preceding Official actions mailed 5-1-02 (Paper No. 13) and 12-10-02 (Paper No. 16) and the reasons set forth above.

Applicants reiterate the arguments regarding Milas and Kanclerz references for the 35 U.S.C. 103(a) rejections of claims 1, 23 and 25-29 and claims 1, 23 and 24 (amendment, p. 16, 17). This is not found persuasive because of the reasons set forth in the preceding Official actions mailed 5-1-02 (Paper No. 13) and 12-10-02 (Paper No. 16) and the reasons set forth above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.